

## Flecainide and Amiodarone: Combined Therapy for Refractory Tachyarrhythmias in Infancy

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**Objectives.** This study assessed the safety and efficacy of combined flecainide and amiodarone therapy in controlling refractory tachyarrhythmias in infants.

**Background.** Single-drug as well as standard combination medical therapy for tachyarrhythmias in infants sometimes fails. In those cases, one may consider interventional therapy. However, this option may carry a high risk of morbidity and mortality in infants. The natural history of tachyarrhythmias in infants often favors eventual resolution and reinforces the importance of selecting an effective medical regimen.

**Methods.** We performed a retrospective analysis of nine infants (median age 2 months) who received combined flecainide and amiodarone therapy for attempted control of refractory tachyarrhythmias. Trough serum drug levels of flecainide were monitored, and 24-h ambulatory electrocardiographic monitoring was used to determine efficacy of therapy.

**Results.** Single-drug treatment with flecainide or amiodarone failed in all of the infants studied. An average of four drugs failed (range one to six) before administration of combined flecainide and amiodarone therapy. During combined therapy, the flecainide

dose was 70 to 110 mg/m<sup>2</sup> per day, and that for amiodarone was 7.5 to 13.5 mg/kg per day for a mean ( $\pm$ SD) of  $9 \pm 2$  days to load and 5 to 12 mg/kg per day as maintenance. Successful control of tachyarrhythmias was demonstrated in seven (78%) of nine infants (95% confidence interval 46% to 99%) (three of three with congenital junctional ectopic tachycardia, three of three with supraventricular tachycardia and one of three with ventricular tachycardia). During combined therapy, flecainide trough levels ranged from 350 to 731 ng/ml. Corrected QT intervals varied from 0.440 to 0.488 ms. No proarrhythmia occurred. None of the infants required a pacemaker, and all had normal left ventricular dimensions and fractional shortening by echocardiography. Eight of nine infants had a structurally normal heart. One infant had surgical correction of an atrioventricular septal defect.

**Conclusions.** Combination therapy with flecainide and amiodarone appears to be safe and effective in controlling refractory tachyarrhythmias in infants. The combination of flecainide and amiodarone may obviate the need for early interventional therapy or may allow delay until the child is older.

(*J Am Coll Cardiol* 1995;25:1195-8)

Conventional medical therapy in infants with supraventricular tachycardias usually includes digoxin, propranolol and flecainide used as single agents or in combination. In addition, amiodarone may be considered a second-line conventional agent by some. For the vast majority of infants these drugs successfully control their tachycardia until it no longer occurs without antiarrhythmic drugs or until the child is of an age and size where interventional therapy with transcatheter radiofrequency ablation is considered safe (1). Currently, most centers advise against the use of transcatheter radiofrequency ablation in infants unless all attempts at medical management of the tachycardia are unsuccessful (2-5).

Likewise, infants with ventricular tachycardia often respond to therapy with propranolol, mexiletine, flecainide or amiodarone. In some cases of incessant ventricular tachycardia, surgical intervention is necessary and may be life-saving, but

the procedure is not without risk and is generally reserved for infants in whom medical therapy has failed (6).

In managing infants with supraventricular tachycardia, it is important to understand that natural history favors eventual resolution in 60% to 90% (7-9). In infants with ventricular tachycardia and no underlying heart disease, the majority have resolution of their tachycardia (10,11). Thus, if a medical regimen can safely and effectively suppress symptomatic tachyarrhythmias in this age group, interventional therapy may not be necessary.

Flecainide and amiodarone used independently have proved effective in the treatment of many tachyarrhythmias in children (12-21). However, single-drug therapy with each of these agents may not always provide acceptable arrhythmia control. Studies in adults have demonstrated safe and effective control of both supraventricular and ventricular tachycardia with combined flecainide and amiodarone therapy (22-25).

### Methods

We retrospectively analyzed the clinical records of nine infants who received combined flecainide and amiodarone therapy. Twenty-four-hour ambulatory electrocardiographic

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Manuscript received April 18, 1994; revised manuscript received October 27, 1994, accepted November 9, 1994.

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**Table 1.** Clinical and Arrhythmia Characteristics of Nine Study Infants

Pt No.	Age/Gender	Cardiac Anatomy	Arrhythmia	Previous Therapy
1	9 d/F	Normal	AET	Dig, Prop, Flec, Amio
2	3.5 mo/M	Normal	AVRT	Dig, Prop, Flec, Amio
3	4.5 mo/F	Normal	CAT	Dig, Proc, Flec, Prop, Amio
4	2 wk/F	Normal	CJET	Prop, Flec
5	2 wk/M	Normal	CJET	Flec
6	2 wk/M	Normal	CJET	Dig, Prop, Flec
7	6 d/M	"Normal," fibrous plaque	VT	Dig, Lido, Proc, Esmo, Amio (IV)
8	8 mo/F	p/o AVSD	VT	Lido, Prop, Proc, Flec, Mex, Amio
9	17 mo/F	"Normal," myocardial tumor	VT	Prop, Proc, Lido, Amio (IV)

AET = atrial ectopic tachycardia; Amio = amiodarone; AVRT = atrioventricular reciprocating tachycardia; AVSD = atrioventricular septal defect; CAT = chaotic atrial tachycardia; CJET = congenital junctional ectopic tachycardia; Dig = digoxin; Esmo = esmolol; F = female; Flec = flecainide; Lido = lidocaine; M = male; Mex = mexiletine; p/o = postoperative; Proc = procainamide; Prop = propranolol; Pt = patient; VT = ventricular tachycardia.

(ECG) monitoring was used to define efficacy. For supraventricular tachycardia and congenital junctional ectopic tachycardia, efficacy of therapy was considered achieved if the tachycardia was eliminated or was slowed to a clinically tolerable rate. In infants with ventricular tachycardia, efficacy was considered achieved if the tachycardia was eliminated. Fluorescence polarization immunoassay was used to measure trough serum drug levels of flecainide 5 half-lives after initiation of therapy and after each dose adjustment. Echocardiograms to assess ventricular function were obtained before and during combination therapy. Left ventricular dimensions and fractional shortening were calculated as previously described (26). Surface ECGs were reviewed before and during combination therapy. The corrected QT interval (QTc) was calculated by normalizing the QT interval for heart rate ( $QTc = QT/\sqrt{RR}$ ) (27).

## Results

**Patient profile.** The age of the infants at diagnosis of their tachyarrhythmia ranged from 6 days to 17 months (median 2 months) (Table 1). Eight of 9 had a structurally normal heart as determined by echocardiography. One infant had surgical correction of an atrioventricular (AV) septal defect. Three of the nine infants had supraventricular tachycardia, including one each with atrial ectopic tachycardia, AV reciprocating tachycardia and chaotic atrial tachycardia. Three infants had congenital junctional ectopic tachycardia, and three had ventricular tachycardia. An average of four antiarrhythmic agents (range one to six) failed before the combined use of flecainide and amiodarone. Treatment with flecainide or amiodarone as single-drug therapy failed in all infants studied.

**Dosages of flecainide and amiodarone.** During combined therapy, the dose of flecainide was 70 to 110 mg/m<sup>2</sup> per day. The starting dose was generally 70 mg/m<sup>2</sup> per day for those infants already receiving amiodarone therapy. For infants who had amiodarone added to their therapy, the flecainide dose

was decreased by one-third. Dosages were adjusted to achieve serum trough levels of 200 to 800 ng/ml, although serum levels <200 ng/ml were accepted if clinical efficacy was met. Flecainide serum trough levels ranged from 350 to 731 ng/ml. Mean dose of amiodarone was 10.6 mg/kg body weight per day (range 7.5 to 13.5) for 9 ± 2 days while loading and 6.7 mg/kg per day (range 5 to 12) as maintenance. Two of the infants with incessant ventricular tachycardia received intravenous amiodarone as previously described (28).

**Response to flecainide and amiodarone therapy.** The combination of flecainide and amiodarone (Table 2) achieved efficacy in seven (78%) of the nine infants (95% confidence interval 46% to 99%). Efficacy was generally observed within 1 to 5 days after initiation of combined therapy. Three of three infants with supraventricular tachycardia and three of three infants with congenital junctional ectopic tachycardia had successful control of their tachyarrhythmia. Patient 5 had congenital junctional ectopic tachycardia at rates of 380 to 400 beats/min. This infant was not maintained in sinus rhythm but was asymptomatic once slowing of the junctional tachycardia rate to 140 to 150 beats/min was achieved. All of the other infants with supraventricular and congenital junctional ectopic tachycardia established sinus rhythm and experienced no tachycardia episodes during combined therapy.

Only one of three infants with ventricular tachycardia responded to flecainide and amiodarone therapy. One infant (Patient 7) developed ventricular tachycardia 2 months after surgical repair of an AV septal defect. After therapy with propranolol, procainamide, flecainide, mexiletine and mexiletine with amiodarone failed, she responded to flecainide and amiodarone combined. Another infant (Patient 8) developed incessant ventricular tachycardia at 6 days of age and had a structurally normal heart by echocardiography. The combination of flecainide and intravenous amiodarone failed to control his tachyarrhythmia but slowed the rate. Because of progressive myocardial decompensation, operative mapping was performed, identifying a fibrous plaque on the right ventricular

**Table 2.** Response and Follow-Up Information

Pt No.	Arrhythmia	Efficacy	Length of Rx	Current Rx	Outcome
1	AET	Yes	7 mo	None	NSR
2	AVRT	Yes	8 mo	Flec	NSR
3	CAT	Yes	6 mo	Flec	NSR
4	CJET	Yes	4 mo	None	NSR
5	CJET	Yes	3 mo	Amio	AJR 140-150 beats/min
6	CJET	Yes	10 mo	None	NSR
7	VT	No	12 h	N/A	Fibrous plaque resection; died 2 days p/o (no VT)
8	VT	Yes	17 mo	Flec/Amio	NSR
9	VT	No	1 wk	None	Tumor resection; NSR

AJR = accelerated junctional rhythm; N/A = not applicable; NSR = normal sinus rhythm; other abbreviations as in Table 1.

free wall. After excision of the plaque, the infant was in sinus rhythm. This infant died on the second postoperative day secondary to a respiratory arrest. Incessant ventricular tachycardia occurred in Patient 9 as well. Again, echocardiography demonstrated a structurally normal heart. After unsuccessful therapy with flecainide and amiodarone, an electrophysiologic study demonstrated the earliest activation of the ventricular tachycardia to be in the posterior left ventricle just below the mitral valve. A hamartoma was surgically removed from the posterior left ventricle below the mitral valve.

**Side effects.** No proarrhythmia occurred, and none of the infants required a pacemaker. The corrected QT intervals varied from 0.440 to 0.488 ms. No side effects occurred that necessitated discontinuing combination therapy.

All of the infants had normal left ventricular dimensions and fractional shortening by echocardiography before combined flecainide and amiodarone therapy, except for Patient 7 with incessant ventricular tachycardia. During combined therapy, all infants continued to demonstrate normal left ventricular dimensions and fractional shortening.

**Follow-up information.** The average length of flecainide and amiodarone therapy in the seven infants with successfully controlled tachyarrhythmias was 6 months (range 3 to 17) (Table 2). Three of seven infants are in sinus rhythm and receive no antiarrhythmic agents. Tachyarrhythmias in three of seven infants are controlled with single-drug therapy, and the remaining infant is in sinus rhythm with combined flecainide and amiodarone therapy. None of the seven infants who achieved effective tachyarrhythmia control with flecainide and amiodarone required interventional therapy.

## Discussion

Combined flecainide and amiodarone therapy has been demonstrated to effectively control refractory tachyarrhythmias in adults. Because amiodarone may increase flecainide plasma levels by ~30%, it is recommended to decrease the initial daily dose of flecainide by 20% to 50% (29-31). In our patients, it appeared reasonable to decrease the initial daily dose of flecainide by one-third when it was used in combina-

tion with amiodarone while flecainide serum trough levels were monitored closely.

**Role of flecainide and amiodarone in infants.** Combined therapy with flecainide and amiodarone successfully controlled tachyarrhythmias that were refractory to all previous medical therapy in seven infants. For a few of these infants this medical regimen may have been life-saving and prevented the need for early interventional therapy. This is most likely the case for three infants with congenital junctional ectopic tachycardia (Patients 4 to 6).

The combination of flecainide and amiodarone appears to be effective for controlling refractory ectopic focus tachycardias, in particular tachycardias with an atrial or junctional focus. Congenital junctional ectopic tachycardia can be very resistant to medical therapy and carries a high risk of mortality if uncontrolled (32,33). All three of the infants in this study with congenital junctional ectopic tachycardia survived, and two are now in sinus rhythm with no antiarrhythmic therapy. Tachyarrhythmia in the remaining infant is well controlled by amiodarone therapy alone with no symptoms and normal echocardiographic findings.

Ventricular tachycardia due to myocardial tumors generally does not respond to standard therapies, although combination antiarrhythmic therapy may be effective in some patients (34). Flecainide and amiodarone did not suppress ventricular tachycardia in two infants in the present study; however, both had slowing of their ventricular tachycardia, allowing stabilization before successful surgical intervention. The infant with ventricular tachycardia who underwent AV septal defect repair did respond to flecainide and amiodarone. Even though the combination therapy was effective in this infant, we do not generally recommend the use of flecainide in children with a structurally abnormal heart.

**Conclusions.** Although the present study included a small number of infants, results with combined flecainide and amiodarone therapy are encouraging. For the infants reported here, combined flecainide and amiodarone therapy appeared to be safe and effective for controlling refractory tachyarrhythmias. Supraventricular tachycardias, in particular those secondary to an ectopic focus mechanism, responded well to this regimen.

The ectopic focus tachycardias are presumably secondary to abnormal automaticity. Because flecainide and amiodarone have different effects on the action potential, it is likely that together they suppress the mechanism responsible for abnormal automaticity in these infants. Without *in vitro* data for this drug combination, it is difficult to speculate on the cellular mechanism responsible. Ventricular tachycardias, although affected by these agents in combination, were not as successfully managed and may ultimately require interventional therapy. In infants with tachyarrhythmias in which conventional medical therapy fails, combined therapy with flecainide and amiodarone should be considered before attempting interventional therapy because the need for interventional therapy may be prevented or delayed until the child is older.

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